

2/pets

10/533517

JC20 Rec'd PCT/PTO 02 MAY 2005

Melatonin daily dosage units

Description

5 The present invention relates to a disposable container
for a medicament or cosmetic agent for topical
application, containing a single dose of melatonin or
of a melatonin derivative which corresponds to a
locally effective dose but which does not cause any
10 systemic effect.

Melatonin-containing agents can be used for various
medical and cosmetic purposes. For example, the document
DE 101 10 418.9 discloses melatonin-containing
15 compositions for topical application on the skin and in
the hair.

The subject of the present invention is a disposable
container for a medicament or cosmetic agent for
20 topical application, containing a single dose of
melatonin or of a melatonin derivative which
corresponds to a locally effective dose but which does
not cause any systemic effect.

25 The disposable container according to the invention
permits application of a dose of melatonin or of a
melatonin derivative which is locally effective but
which causes no undesired change in the normal
melatonin plasma level. The single dose of melatonin or
30 of melatonin derivative which is applied according to
the invention causes no significant elevation of the
melatonin plasma level for example.

The expression "melatonin or melatonin derivative", as
35 it is used in the context of this application, includes
melatonin and/or melatonin derivatives and salts,
esters or complexes thereof. Preferred melatonin
derivatives include, for example, 5-methoxytryptamine,
5-methoxytryptophan, 5-methoxytryptophol, 5-methoxy-

indole-3-acetic acid and 6-hydroxymelatonin.

The single dose according to the invention represents a dose which permits a positive cosmetic and/or
5 therapeutic effect without significant changes in the plasma level. According to the invention, a single dose of from approximately 0.001 to approximately 1.0 mg of melatonin is preferred, and more preferably a single
10 dose of from approximately 0.01 to approximately 0.2 mg of melatonin. Depending on the application area or the intended use of the agent, a single dose can be applied once or several times daily. In a preferred embodiment, the single dose corresponds to a daily dose, particularly preferably a daily dose to be used in the
15 evenings.

The medicament or cosmetic agent is preferably present as a liquid formulation. Examples of suitable formulations for topical application of the agent are
20 solutions, suspensions, emulsions, microemulsions, nanosystems, creams, gels, lotions, sprays, foams or ointments, and any other formulation which can be applied topically. The agent is particularly preferably provided in the form of a cosmetic solution.

25 Depending on its intended use, the medicament or cosmetic agent contained in the disposable container according to the invention can have different concentrations of melatonin or of a melatonin
30 derivative. The agent preferably contains a concentration of approximately 0.001 to approximately 0.01% (by weight), more preferably approximately 0.003 to 0.004% (by weight) of melatonin or of a melatonin derivative. A particularly preferred concentration is
35 approximately 0.0033% (by weight).

In one embodiment, the therapeutic or cosmetic agent contains melatonin or a melatonin derivative as sole active substance. The agent can, however, also contain

one or more further active substances such as vitamin A, vitamin A acid or other vitamin A derivatives, biotin and/or ginkgo biloba.

5 In a preferred embodiment, the medicament or cosmetic agent contains a combination of the active substances melatonin or melatonin derivative with biotin and/or ginkgo biloba. The active substances in this embodiment can be in different dosages. A particularly preferred
10 dosage of this combination is from approximately 0.05 to approximately 0.2 mg, particularly preferably approximately 0.1 mg of melatonin or melatonin derivative, from approximately 0.2 to approximately 0.4 mg, particularly preferably approximately 0.3 mg of biotin,
15 and from approximately 1.3 to approximately 1.7 mg, particularly preferably approximately 1.5 mg of ginkgo biloba. Ginkgo biloba can in this case be contained for example as an extract, in particular as a dry extract, and/or in the form of one or more ingredients.

20 In a further preferred embodiment, the agent contains a combination of the active substances melatonin or melatonin derivative and vitamin A, vitamin A acid or another derivative of vitamin A. In this preferred
25 active substance combination, the dosage of melatonin or melatonin derivative is preferably from approximately 0.05 to 0.2 mg, particularly preferably approximately 0.1 mg of melatonin.

30 The medicament or cosmetic agent can also contain one or more cosmetic and/or pharmaceutical auxiliaries or additives, for example thickeners, minerals or perfumes.

35 The composition according to the invention can be used to promote hair growth, in particular to prevent and/or treat alopecia in men or in women. Particularly preferred indications are male pattern androgenetic alopecia, female pattern androgenetic alopecia, male pattern diffuse

alopecia and female pattern diffuse alopecia.

Depending on the intended application or use, the disposable container according to the invention can contain different volumes of the medicament or cosmetic agent. In a preferred embodiment, the disposable container contains approximately 2.5 to approximately 3.5 ml, preferably approximately 2.9 to approximately 3.2 ml of the agent. A particularly preferred volume is approximately 3.0 ml.

The therapeutic or cosmetic agent can be filled into the container using any suitable method known in the prior art. The agent is preferably filled into the container under GMP conditions. In this way it is possible to ensure that the agent is sterile and that, when the agent is applied, no problems arise in respect of bacterial contamination.

The disposable container according to the invention can in principle be made of any desired material, in particular a material approved for packaging of food products and pharmaceutical products. Examples of preferred materials are plastics and mixtures of plastics. Examples of particularly suitable plastics are polyethylene, polyvinyl chloride, polystyrene, polypropylene, polycycloolefins or mixtures or copolymers thereof, with particular preference being given to polyethylene or polycycloolefins.

Depending on its desired outward appearance, the disposable container can be transparent, non-transparent, colorless or colored. Any desired dyes can for example be added to the plastic in order to obtain a colored container. A non-transparent container is preferred for use if the agent contains light-sensitive substances, because a non-transparent container additionally affords protection from light.

The disposable container according to the invention can in principle have any desired shape. Examples of preferred containers are shown in Figures 1 and 2. A suitable disposable container preferably comprises a
5 part in which the agent is contained, and a disposable closure piece which is connected to the lower part via a predetermined break line.

Simple and safe handling of the container is
10 advantageously ensured by the fact that it preferably has, on its head, a disposable closure piece which is opened by turning it. The container can thus be easily opened. In addition, after opening, the agent can emerge only if pressure is applied. This pressure can
15 for example be exerted by hand during the application. This property allows the user to correctly dose the agent and position it in a targeted manner. If the agent is to be applied to the scalp or hair, the opened container can be guided directly through the hair like
20 a comb. This permits straightforward and safe handling of the container and correct dosing of the agent.

Depending on the intended use, the disposable container carries lettering either printed on or embossed and/or
25 is provided with a label.

Two or more disposable containers can furthermore be connected to one another in a detachable manner. For example, 5 or 10 containers are preferably connected to
30 one another and form an arrangement. A container or an arrangement of containers can also be packed, preferably in a lightproof package, particularly preferably in an aluminum bag for example.

35 The expression "aluminum bag", as it is used here, includes bags made of aluminum and also bags which for example are coated with aluminum on the outside or inside. For example, bags made of one or more layers of plastic and/or paper can be coated with aluminum. A

preferred bag comprises, for example, an aluminum-containing laminated foil which additionally includes polyethylene, polyester and/or paper.

- 5 A package, in particular a lightproof package, permits storage over a fairly long period of time without loss of efficacy of the agent. Furthermore, such a package can provide protection against gas loss.
- 10 Depending on the intended use, an aluminum bag in which one or more disposable containers are packed can be printed on and/or provided with a label.

In a further embodiment of the invention, a package
15 unit comprising several arrangements of disposable containers is provided.

The invention is further explained by attached Figures 1 and 2 and examples.

20 Fig. 1 shows an arrangement of 5 disposable containers connected to one another in a detachable manner and in a preferred configuration.

1A shows a front view, 1B a plan view, 1C a
25 side view, and 1D a perspective view obliquely from above.

Fig. 2A shows a front view of an individual disposable container in a preferred configuration.

30 2B shows a front view of an arrangement of 10 disposable containers connected to one another in a detachable manner, 2C shows a side view, and 2D shows a plan view of said arrangement.

35 Examples

Example 1: Composition of a formulation according to the invention containing melatonin, ginkgo biloba and biotin as active substances

The composition contains 0.05% by weight of ginkgo biloba dry extract, 0.01% by weight of biotin, 0.0033% by weight of melatonin and other additives, water, and ethanol. The pH of the composition is between 3.5 and 4.

Example 2: Clinical study

The composition described in Example 1 was tested on 8 healthy female patients in a randomized double-blind study with placebo control and a crossover design. The daily dose was 0.1 mg of melatonin (3 ml of the composition) which was applied to the scalp each day before bedtime, for a period of 14 days.

Urine and blood samples were taken from the patients and were assayed for melatonin and the metabolite 6-hydroxymelatonin sulfate.

It was found that the melatonin plasma profiles of the patients treated with melatonin or placebo corresponded to the concentration/time profiles described in the literature for endogenous melatonin. This confirms that topical application of the melatonin-containing composition for 14 days does not alter endogenous melatonin secretion.

Administration of the composition for 14 days did not increase the plasma concentration of melatonin, or the concentration of 6-hydroxymelatonin sulfate in urine, above physiological concentrations. Topical application of the melatonin-containing composition was not associated with side effects. Nor were any effects found on reaction times or on cortical excitation parameters.

All things considered, it must be concluded that administration of the composition does not induce any

systemic effects.